ProHeart® 6 Briefing Package
Veterinary Medical Advisory Committee
March 24, 2010

Description of ProHeart® 6

ProHeart® 6 (moxidectin) is a sustained (slow) release (SR) formulation of moxidectin-impregnated microspheres injected subcutaneously, providing single dose continuous protection against heartworm disease, caused by *Dirofilaria immitis*, for six months. ProHeart 6 is also indicated for the treatment of existing larval and adult hookworm (*Ancylostoma caninum* and *Uncinaria stenocephala*) infections.

ProHeart 6 consists of two separate vials. Vial 1 contains 10% moxidectin sterile microspheres and Vial 2 contains a specifically formulated sterile vehicle for constitution with Vial 1. Each mL of constituted drug product contains 3.4 mg moxidectin, 3.1% glyceryl tristearate, 2.4% hydroxypropyl methylcellulose, 0.87% sodium chloride, 0.17% methylparaben, 0.02% propylparaben and 0.001% butylated hydroxytoluene.

ProHeart 6 is administered (by a veterinarian) subcutaneously in the left or right side of the dorsum of the neck cranial to the scapula. The subcutaneous dose is 0.05 mL of constituted suspension/kg body weight (0.0227 mL/lb). ProHeart 6 is administered using an appropriate sized syringe fitted with a 18G or 20G needle, alternating injections in the sides of the dorsum of the neck between injections.

ProHeart 6 is fully described in the product label provided in **Attachment 1**.

Background and Objectives of the VMAC

Since the drug was recalled in September, 2004, the manufacturers (Fort Dodge Animal Health) conducted studies to further evaluate the safety profile of ProHeart® 6 and to investigate the reported adverse events. These studies included additional toxicologic and pharmacologic evaluations which suggested the potential allergenic nature of some of the residual solvents that are utilized in the manufacture of ProHeart® 6. As a result, Fort Dodge changed the manufacturing specifications for ProHeart® 6 and marketed the modified product in international markets. In the years following this change, there was a decline in the adverse event reporting in international markets. The results of the toxicologic studies coupled with the lower adverse event frequency in international markets were factors in FDA's decision to concur with Fort Dodge's restricted return of ProHeart® 6 to the U.S. market under a risk minimization and restricted distribution program (RiskMAP) plan in June, 2008. In addition to the plan, based on post-approval experience, the ProHeart® 6 label and Client Information Sheet were revised to include updated safety information.

ProHeart 6 is the first veterinary drug marketed under a RiskMAP that allows veterinarians to weigh the risk of heartworm disease in their canine patients with the benefits of a 6-month injection that maximizes protection.

The ProHeart 6 RiskMAP was modeled on RiskMAPs in place for some human pharmaceutical products in the US and provided for the collection and evaluation of pharmacovigilance information, including the use of ProHeart 6 without the confounding effect of concurrent vaccinations. Since implementation of the RiskMAP, the adverse reaction rate for ProHeart® 6 was ~3 adverse reactions per 10,000 doses distributed. This included all of the reports received for ProHeart 6 regardless of causality or association with the product.

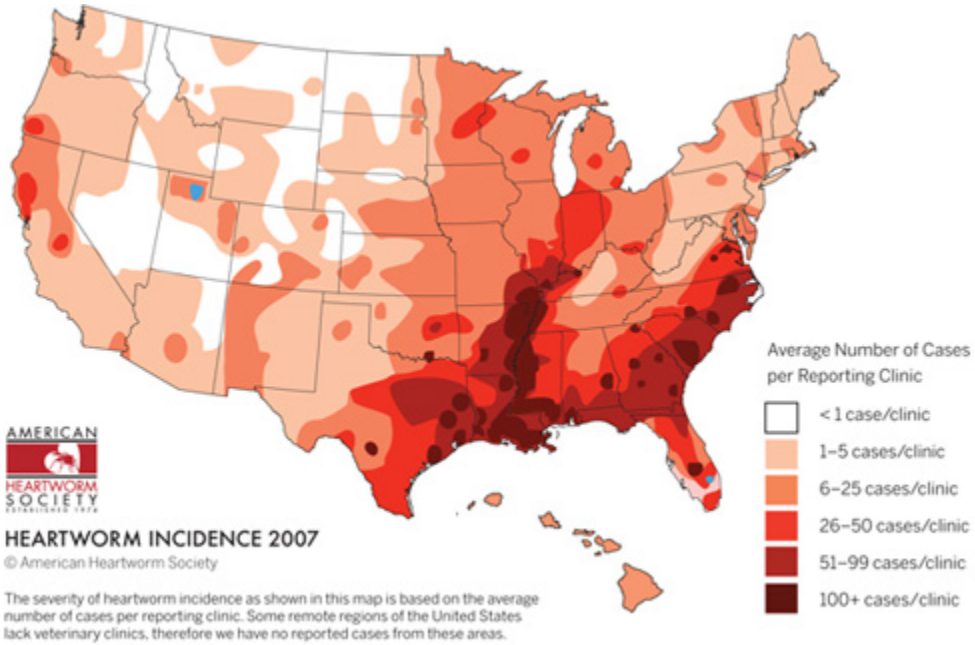
In October, 2009 Pfizer Animal Health acquired Wyeth. Fort Dodge Animal Health was a Division of Wyeth and has been incorporated into Pfizer Animal Health (PAH). PAH has assumed all responsibilities and commitments of the ProHeart 6 RiskMAP.

The terms of the RiskMAP provide for modifications based on new scientific information, including pharmacovigilance. The objective of this VMAC meeting is to review the results of the RiskMAP and consider changes to the ProHeart 6 label and RiskMAP.

Backgound on Heartworm Disease and Prevention
(Source: American Heartworm Society website http://www.heartwormsociety.org/)

Heartworm disease is a serious and potentially fatal condition caused by parasitic worms living in the arteries of the lungs and occasionally in the right side of the heart of dogs, cats and other species of mammals, including wolves, foxes, ferrets, sea lions and (in rare instances) humans. Dogs and cats of any age or breed are susceptible to infection.

Heartworm disease has been reported in all 50 states. The map below shows particularly endemic areas based on the number of cases reported by clinics.



Heartworm infection is identified as a worldwide clinical problem. Despite improved diagnostic methods, effective preventives and increasing awareness among veterinary professionals and pet owners, cases of heartworm infection continue to appear in pets around the world.

Heartworm Life Cycle

First, adult female heartworms release their young, called microfilariae, into an animal's bloodstream. Then, mosquitoes become infected with microfilariae while taking blood meal from the infected animal. During the next 10 to 14 days, the microfilariae mature to the infective larval stage within the mosquito. After that, the mosquito bites another dog, cat or other susceptible animal, and the infective larvae enter through the bite wound. It then takes a little over 6 months for the infective larvae to mature into adult worms. In dogs, the worms may live for up to 7 years. Microfilariae cannot mature into adult heartworms without first passing through a mosquito.

Recently infected dogs may exhibit no signs of the disease, while heavily infected dogs may eventually show clinical signs, including a mild, persistent cough, reluctance to move or exercise, fatigue after only moderate exercise, reduced appetite and weight loss.

Heartworm infection in apparently healthy animals is usually detected with blood tests for either a heartworm-specific antigen or microfilariae, although neither test is consistently positive until about seven months after infection has occurred. Heartworm infection may also occasionally be detected through ultrasound and/or x-ray images of the heart and lungs, although these tests are usually used in animals already known to be infected.

Prevention

Heartworm prevention is safe, easy and inexpensive. There are a variety of options for preventing heartworm infection in both dogs and cats, including monthly tablets and chewables, monthly topicals and a six-month injectable product (ProHeart 6) available only for dogs. All of these methods are extremely effective, and when administered properly on a timely schedule, heartworm infection can be prevented. These medications interrupt heartworm development before adult worms reach the lungs and cause disease.

Heartworm Chemoprophylaxis

Options for effective chemoprophylaxis in the US include several drugs administered either in oral, topical or parenteral formulations on a monthly or six-month interval. Before starting a prophylactic regime, all mature dogs that may have been infected at least seven months earlier should be antigen tested, and in appropriate instances, also tested for microfilariae. It is strategically important to determine heartworm status before starting chemoprophylaxis for the first time. This will avoid unnecessary delay in detecting subclinical infections and potential confusion concerning effectiveness of the prevention program, if a pre-existing infection becomes evident after beginning chemoprophylaxis (e.g. chemoprophylaxis initiated during the pre-patent period).

Benefits of ProHeart 6

Since all pharmaceutical products pose the potential for adverse events, the benefits of chemoprophylaxis must be weighed against the risks. Heartworm disease is potentially life threatening and treating infected dogs is a complicated and expensive process. To prevent heartworm disease, most products must be administered by the pet owners on a monthly basis. Unfortunately, many pet owners forget to administer the heartworm preventative products according to the required treatment schedule. In addition, products must be properly administered, which can be problematic for some pet owners. The potential also exists for an oral product to be spit out or vomited. Missing a monthly dose by more than 30 days greatly increases the probability for heartworm infection to occur. The primary benefit of ProHeart 6 is compliance. ProHeart 6 is administered subcutaneously every six months by a veterinarian. This ensures ProHeart 6 is professionally administered in accordance with the required treatment regimen.

Risk Minimization Action Plan (RiskMAP)

The purpose of this RiskMAP was to manage the re-introduction of ProHeart 6 to provide the benefit of 6-month continuous heartworm prevention while minimizing risk to dogs.

The ProHeart 6 RiskMAP consists of an education and communication plan for veterinarians and dog owners, restricted access to the product for trained veterinarians only, enhanced adverse event (AE) reporting requirements and label changes. ProHeart 6 continues to be provided in accordance with the RiskMAP.

By setting forth a proactive plan of risk minimization activities, the potential for harm associated with use of ProHeart 6 was reduced and the benefits of 6-month continuous protection are extended to individual dogs. In addition, the RiskMAP allows for clearer characterization of the safety profile of ProHeart 6 by eliminating confounding factors such as adverse reactions associated with concurrent vaccination. Regular evaluation of the RiskMAP ensures that captured adverse events are reviewed and analyzed in a timely manner and, if appropriate, mitigated by revising the guidelines for veterinarians to follow when using ProHeart 6. The objectives of the RiskMAP include:

Veterinarians:

- Provide the reasons for the recall and the new information that has resulted in the restricted return to market.
- Describe the label changes and the reasons for them, including the restriction on concurrent vaccination.
- Describe the requirements for enrollment in the ProHeart 6 prescribing program.
- Describe the need to restrict initial treatment to healthy dogs between the ages of 6 months and 7 years.
- Describe the need to collect blood samples prior to treatment.
- Understand the need for close monitoring of treated dogs for suspected adverse events and for reporting these promptly to PAH.

- Provide owners with a client information sheet, answer owners' questions, and obtain a signed informed consent form before each animal is treated.

Dog Owners:

- Provide the risks and benefits of ProHeart 6 through a Client Information Sheet.
- Sign the Informed Consent Form.
- Have open communication with their veterinarian about suspected adverse events.

Pfizer Animal Health (Previously Fort Dodge Animal Health):

- Implement a comprehensive risk minimization program that communicates new label information to veterinarians.
- Implement education and registration requirements for veterinarians prior to purchase of ProHeart 6.
- Implement monthly (the official version is the hard copy Form 1932) submission of all suspected adverse events to CVM as reported to PAH.
- Identify and interpret possible trends in adverse event reporting and communicate to CVM on a regular basis.

Updates to the RiskMAP are discussed with CVM on a quarterly basis or as needed, and include feedback received from veterinarians. Adverse events are reported to CVM monthly. Risk minimization activities may be terminated or modified and alternative methods adopted based on discussions with the CVM.

Details of the RiskMAP

The company, working with the CVM, developed a comprehensive RiskMAP program encompassing:

- A revised product label;
- A comprehensive educational program and communication plan;
- Distribution of the product restricted to veterinarians who have completed training;
- A comprehensive pharmacovigilance system to monitor adverse events; and
- Frequent communication with CVM.

A comprehensive educational program and communication plan were developed as part of the RiskMAP. A complete copy of the RiskMAP and all the associated materials is provided in **Appendix A**.

Revised Product Label

The product label is the cornerstone of risk minimization for all FDA-approved products. The revised approved package insert, provided as **Attachment 1**, includes additional detailed instructions for use, dosage and administration information, and precautions and warnings associated with the product. The following specific information was added to the label:

- **Warning: "Do not administer ProHeart® 6 within 1 month of vaccinations."**

- **Warning: "ProHeart 6 should be administered with caution in dogs with pre-existing allergic disease, including food allergy, atopy, and flea allergy dermatitis." In some cases, anaphylactic reactions have resulted in liver disease and death. Anaphylactic and anaphylactoid reactions should be treated immediately with the same measures used to treat hypersensitivity reactions to vaccines and other injectable products.**

- **Warning: "Do not to administer ProHeart® 6 to dogs who are sick, debilitated, underweight, or who have a history of weight loss.**

- **Precautions: Caution should be used when administering ProHeart 6 to heartworm positive dogs (See ADVERSE REACTIONS).**

- **The Adverse Reaction section of the label was revised to include the following:**

  In field studies, the following adverse reactions were observed in dogs treated with ProHeart® 6: anaphylaxis, vomiting, diarrhea (with and without blood), listlessness, weight loss, seizures, injection site pruritus, and elevated body temperature. Dogs with clinically significant weight loss (>10%) were more likely to experience a severe adverse reaction.

  In a laboratory effectiveness study, dogs with 4- and 6-month-old heartworm infections experienced vomiting, lethargy and bloody diarrhea. These signs were more severe in the dogs with 4-month-old heartworm infections, including one dog that was recumbent and required supportive care, than in the dogs with older (6-month-old) infections.

- **The label's Post-Approval Experience section was updated to include adverse reactions, such as liver and blood disorders:**

  Post-Approval Experience (March 2008): The following adverse reactions are based on voluntary post-approval drug experience reporting. The categories are listed in decreasing order of frequency by body system:
  General: Anaphylaxis/toid reactions, depression/lethargy, anorexia, fever, weight loss.
  Gastrointestinal: Vomiting (with and without blood), diarrhea (with and without blood), hypersalivation.
  Neurological: Convulsions, ataxia, trembling, hind limb paresis
  Dermatological: Urticaria, head/facial edema, injection site pruritus/swelling, erythema multiforme.
  Hematological: Immune-mediated hemolytic anemia, leukocytosis, immune-mediated thrombocytopenia
  Hepatic: Elevated liver enzymes, hepatopathy, hypoproteinemia, hyperbilirubinemia.
  Respiratory: Dyspnea, polypnea, coughing.
  Cardiopulmonary signs such as coughing and dyspnea may occur in heartworm-positive dogs treated with ProHeart 6.

In rare situations, death has been reported as an outcome of the adverse events listed above.
To report suspected adverse reactions or to obtain technical assistance, call (800) 533-8536.

Dear Doctor Letter

A "Dear Doctor" letter was issued by FDAH announcing the return of ProHeart 6 to the U.S. market and outlining the company's education and training requirements for veterinarians to prescribe ProHeart 6. This letter invited veterinarians to attend the education and training program and provided instructions for participation.

Web-based Training

Veterinarian completion of the Web-based training and registration is one of the conditions of access to ProHeart 6. This module includes:

- New information regarding the safety of ProHeart 6;
- Description of the revised ProHeart 6 label, and Client Information Sheet;
- Listing and description of the serious adverse events of concern to CVM. These are death, anaphylaxis, convulsions, hepatopathy, immune-mediated anemia, immune-mediated thrombocytopenia and weight loss;
- Conditions of ProHeart 6 use, including age eligibility, pre-existing health status, collection of CBC/chemistry panel, RBC and platelet count prior to treatment, and exclusion of concurrent vaccination;
- Requirement for enrollment in the ProHeart 6 prescribing program;
- Requirement to provide the Client Information Sheet to the dog owner, and to answer questions;
- Requirement for a signed Informed Consent form by the dog owner, which will be maintained in the dog's medical record by the veterinarian; and
- Requirement to report all suspected adverse events to the Company.

Client Information Sheet

In order for dog owners to have their dog treated with ProHeart 6, they are informed of the benefits and risks by reading a Client Information Sheet, which includes information about mode of action of sustained-release drugs, safety and effectiveness information, precautions, and potential adverse events in a user-friendly "questions and answers" format.

Informed Consent

Owners must read and sign the informed consent prior to the initial administration of ProHeart 6.

Informational Websites

Separate websites for veterinarians and dog owners are available as a communication and education resource. These are http://www.ProHeart6dvm.com and http://www.ProHeart6.com, for veterinarians and owners, respectively.

Toll-Free Telephone Number

A toll-free number is available for veterinarians and dog owners. This allows direct contact with PAH Veterinary Medical Investigation and Product Support (VMIPS) to provide a resource to answer questions and for reporting suspected adverse events.

Restricted Distribution

To become an authorized user of ProHeart 6, veterinarians have to register with PAH confirming they have read the new label, the conditions of use, the requirements to provide the owner with the client information sheet and obtain signed informed consent, as well as PAH's requirement to report adverse events.

Comprehensive Pharmacovigilance Program

PAH has a comprehensive validated pharmacovigilance system for the collection, verification, evaluation and reporting of adverse events associated with the use of marketed products. This is in accordance with worldwide regulatory reporting requirements for drug safety. New safety information is collected, reviewed and analyzed on an ongoing basis from multiple sources, including spontaneous reports, reports from regulatory agencies outside the United States, and reports from published literature.

All adverse events are recorded using the validated PVWorks software program by PAH's VMIPS group. All adverse event reports, including ProHeart adverse events, are submitted to CVM by the PAH Regulatory Affairs group in accordance with 21 CFR 514.80. Adverse events categorized as "serious, unexpected" are submitted to CVM as 15-day alert reports. Certain adverse event reports are subject to special reporting processes, and reported as 15 day reports even though they are listed on the label. These adverse events are: anaphylaxis, convulsions, immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, liver disease and death. Adverse events normally categorized as "periodic" are also submitted in the monthly Special Drug Experience Report. In addition to these statutory reporting requirements, PAH provides completed "Form 1932's" for ProHeart 6 adverse event reports to CVM electronically on CD-ROM on a monthly basis. Evaluation of adverse events reports as a function of ProHeart 6 lot manufacturing parameters are also conducted.

Each individual case is reviewed as it is received. At the end of each quarter, the collected information is evaluated by the nature and number of adverse events in relation to the number of doses sold. The adverse event data are evaluated on a monthly basis to identify and interpret trends of adverse events. These reporting rates are described for the adverse events considered to be possibly related to ProHeart 6 administration.

As part of the evaluation of adverse events, PAH works with the reporting veterinarian to ensure appropriate diagnostic work is conducted in relation to the clinical signs reported. This may include testing by a nationally accessible diagnostic laboratory that uses standardized testing techniques.

Frequent Communication with CVM

The following is communicated to the CVM:

- The completed "Form 1932's" are submitted monthly to CVM by PAH's Regulatory Affairs department via hard copy and CD-ROM.
- The pertinent manufacturing parameters were also initially included, but with CVM's consent most were removed after the RiskMAP was in place for one year:
    - Lot number (finished product (microsphere and vehicle) and API)
    - Certificate of analysis for each lot
    - Certificate of analysis from the terminal sterilization process
    - Impurities/degradation products associated with each microsphere lot
    - Correlate dose to specific lot
    - Lot age at time of product administration.
    - Stability monitoring as requested by CVM
- Trends identified when adverse event data are evaluated.
- Review RiskMAP data and interpretation quarterly or as needed with CVM to determine if adjustments are warranted.
- Periodically review the RiskMAP and evaluate and propose label changes and modifications to or termination of the RiskMAP.

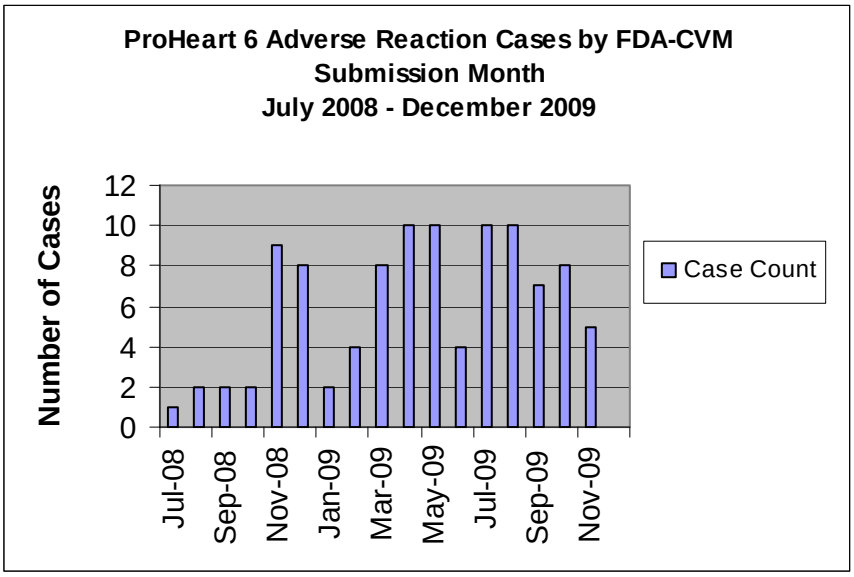
Adverse Drug Event (ADE) Reporting

Since the RiskMAP had been in place, more than 6,500 veterinarians representing more than 4,000 clinics took the ProHeart 6 RiskMAP training and were certified users of the product in the first 18 months.

RiskMAP Results for First 18 Months

During the first 18 months since ProHeart 6 was reintroduced in accordance with the RiskMAP, there were over 300,000 doses distributed. **Figure 1** shows the distribution of adverse reaction cases (excluding lack of effectiveness reports) by CVM submission month since reintroduction of the product. Consistently, there have been approximately 10 cases or less submitted monthly. This case count includes all adverse reactions regardless of causality assessment or association with the product.

Figure 1

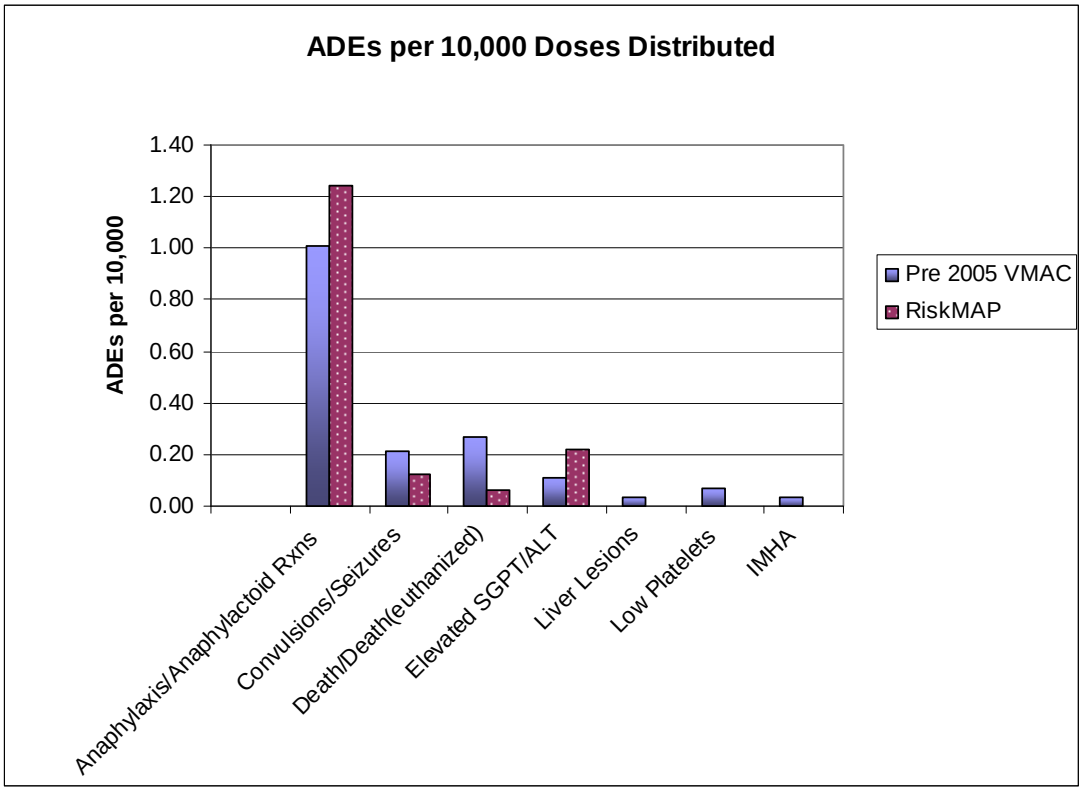


CVM conducted a thorough analysis and evaluation of the U.S. pharmacovigilance data for the first 18 months after ProHeart 6 was returned to the market under the RiskMAP. Figure 2 (table) and Figure 3 (graph) show the RiskMAP ADE rate per 10,000 doses distributed as compared to the safety signals reviewed during the January 2005 VMAC. These cases had a causality assessment of possibly or probably drug related.

Figure 2

	ADE Rate per 10,000 Doses Distributed as reported by Sponsor, Estimated on the Basis of a 20 kg Dog	
	Unrestricted Marketing in US 6/1/01 - 9/1/04	RiskMAP Marketing in US 6/16/08 - 12/15/09
Sponsor Reported Number of Doses Distributed*	18,000,000	321,290
Death	0.27	0.06
Anaphylaxis/Anaphylactoid	1.01	1.24
Seizures	0.21	0.12
Liver Lesions	0.04	0.00
Elevated SGPT/ALT	0.11	0.22
Low Platelets	0.07	0.00
IMHA	0.04	0.00
*number of vials distributed x 19 doses/vial based on an average weight 20 kg dog		

Figure 3
ADE Rate per 10,000 Doses Distributed as reported by Sponsor, Estimated on the Basis of a 20 kg Dog



The following is a summary of the adverse events:

- For the 18-month time period (16Jun2008 – 15Dec 2009): 102 adverse reactions; 30 lack of effectiveness cases and 1 asymptomatic human exposure report was received for ProHeart 6.

- The age range of the affected dogs was 6 months – 9 years of age with a mean of 3.1 years. The weight range of the dogs was 5-101 lbs with a mean of 45.8 lbs. The distribution of breeds in the ADE database reflected breed popularity in the general population. Males and females were equally represented in the ADE reports.

- Forty out of 102 adverse reactions involved anaphylaxis/anaphylactoid reactions and included 2 reports of anaphylactic shock. The reactions associated with the product occurred within 24 hours of administration, most commonly less than 2 hours following administration. The reactions included facial swelling, with or without erythema, urticaria, and pruritus. Occasionally, vomiting, diarrhea, lethargy and fever accompanied these signs. Recovery with treatment, including diphenhydramine, dexamethasone, and prednisone, generally occurred within 24 hours. An important comparison is that CVM reviewed 20 reports of

death by anaphylactic shock in 2004; conversely, none of the anaphylaxis reactions reported during the RiskMAP resulted in death.

- Thirty-four out of 102 adverse reaction cases involved cases associated with gastrointestinal signs. These cases included reports of any of the following clinical signs: hypersalivation, anorexia, vomiting, diarrhea, vomiting and diarrhea, hemorrhagic diarrhea and lethargy. The onset of signs was typically $\leq$ 1 day and commonly < 1 hour post injection. The majority of cases recovered in less than 4 days. Cases with an onset longer than 3 days and with a duration greater than 4 days were generally determined to be due to an underlying medical condition. Some of the cases received supportive treatment and all of the cases recovered.

- No cases of hemolytic anemia were reported. Two cases of low platelets were reported but they were not considered drug related and the animals recovered uneventfully.

- Four cases of seizures were reported and scored as possibly drug related. They are summarized as follows:
    - One case (onset 6 days)
        - recovered without intervention
    - One case (onset 28 days)
        - lost to follow-up
    - One case (onset 52 days)
        - medicated with phenobarbital
    - One case (onset 60 days)
        - lost to follow-up
    - Cannot rule out epilepsy or other causes

- Eight cases of death (See Appendix B for the ADE reports) were reported. All cases had alternative etiologies as a likely cause of mortality. Using the modified Kramer algorithm scoring system, 2 cases were considered possibly drug related. The following etiologies were identified:

    - Neoplasia (4 cases)
        - Lymphoma - euthanasia
        - Bile duct mass/splenomegaly, died after Sx
        - Metastatic sarcoma – euthanasia
        - Ruptured splenic mass
    - Cardiomyopathy (2 cases)
    - Parvovirus infection (possibly drug related score)
    - Liver failure 5 days post-treatment – pre-existing liver disease/phenobarbitol toxicity – euthanasia (possibly drug related score)

- No cases of liver lesions were reported. There were 8 cases of elevated ALT liver enzyme reported. One case was not scored as possibly/probably drug related, five cases had mild enzyme elevations, and some were confounded by other factors. No apparent association with PH6 administration could be made.

- Eight cases received concomitant vaccines but there was insufficient information to assess the possible interaction with ProHeart 6. They are summarized as follows:
    - 3 cases mild anaphylaxis signs
    - 1 case seizure
    - 2 cases neurologic signs
    - 1 case lack of effectiveness
    - 1 case - no assessment possible (info lacking)

- There were 30 reports of lack of effectiveness. The majority of these cases represented pre-existing disease or possible pre-patent infections existing prior to ProHeart® 6 administration. All but one of the LOE cases originated from heartworm endemic states. One case out of 30 was assessed as probably associated with ProHeart® 6 and this case could possibly be due to a pre-patent infection at the time of the 1st injection.

Questions for the VMAC Committee

VMAC question #1:

1. Based on the data generated by the ProHeart® 6 RiskMAP, should the RiskMAP and/or the product labeling be modified in regards to the following 2 items?

- The following statement is currently contained in the WARNINGS section of the product label: "Do not administer ProHeart® 6 within 1 month of vaccinations." Based on the data presented, should the statement be modified as a PRECAUTION such as "Use with caution when administering ProHeart® 6 within 1 month of vaccinations. Adverse reactions, including anaphylaxis, have been reported following the concomitant use of ProHeart 6 and vaccinations."?
- The current RiskMAP requires the collection of a CBC/chemistry panel, prior to product administration. Should this requirement be modified in the RiskMAP and added to the label in a statement such as "Appropriate laboratory testing to establish hematological and serum biochemical baseline data is recommended prior to administration of ProHeart 6."

VMAC question #2:

2. Based on the information and data presented today, are there any additional modifications, additions or deletions to the ProHeart 6 RiskMAP and/or labeling you suggest?

Attachments:

Attachment 1. ProHeart 6 Label

Appendices:

Appendix A. RiskMAP
Appendix B. ADE case reports of death